


SYSTEMATIC REVIEWS (WITH OR WITHOUT META-ANALYSES)

A systematic review of the effectiveness and safety of droperidol for pediatric agitation in acute care settings

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Abstract

Objective: Agitation in children in acute care settings poses significant patient and staff safety concerns. While behavioral approaches are central to reducing agitation and oral medications are preferred, parenteral medications are used when necessary to promote safety. The goal of this systematic review was to evaluate the effectiveness and safety of an ultra-short-acting parenteral medication, droperidol, for the management of acute, severe agitation in children in acute care settings.

Methods: A systematic review of randomized controlled trials, observational studies, and case series/reports examined the effectiveness and safety of parenteral droperidol for management of acute agitation in patients ≤ 21 years old in acute care settings. Effectiveness outcomes included time to sedation and need for a subsequent dose of medication. Safety outcomes were adverse effects such as QTc prolongation, hypotension, respiratory depression, and dystonic reactions.

Results: A total of 431 unique articles were identified. Six articles met inclusion criteria: two in the prehospital setting, one in the emergency department, and three in the inpatient hospital setting. The articles included a prospective observational study, three retrospective observational studies, and two case reports. The largest study reported a median time to sedation of 14 min (interquartile range 10–20 min); other studies reported a time to sedation of 15 min or less. Across studies, 8%–22%

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of patients required a second dose of medication for ongoing agitation. The most frequent adverse effects were dystonic reactions and transient hypotension. One patient had QTc prolongation and another developed respiratory depression, but both had significant comorbidities that may have contributed. The risk of bias in included studies ranged from moderate to critical.

Conclusions: Existing data on droperidol for management of acute agitation in children suggest that droperidol is both effective and safe for acute, severe agitation in children. Data are limited by study designs that may introduce bias.

BACKGROUND AND IMPORTANCE

Acute agitation in children in the hospital setting poses a serious safety risk to patients and staff. In a national survey of pediatric hospitalists and pediatric psychiatry consultants, most encountered acute agitation as frequently as every week.¹ As pediatric mental health visits to U.S. emergency departments (EDs) have risen over the past decade,^{2,3} visits involving the use of intramuscular medications for agitation have increased threefold.⁴ Nevertheless, a paucity of evidence on medication efficacy and safety is available to guide the choice of medication for acute agitation in children.⁵

Behavioral approaches such as verbal deescalation are central to reducing acute agitation, but when these fail, medications may be used to reduce acute agitation and decrease the risk of harm to self or others.⁶ Classes of medications commonly used to manage pediatric acute agitation include benzodiazepines and antipsychotics, with antihistamines sometimes used as adjuncts to prevent extrapyramidal side effects.⁴ Oral medications, whenever possible, are the preferred route of delivery for medication to treat acute agitation.⁶ However, response rates to oral medications are generally low, varying from 30% (loxapine) to 53% (quetiapine) within 60min of administration among adolescents with acute agitation in the ED.⁷ For children who fail to respond to oral medications or who refuse to take them, intramuscular or intravenous medications may be used to manage acute agitation.

Droperidol is a high-potency butyrophenone, first-generation antipsychotic that was approved by the U.S. Food and Drug Administration (FDA) as an antiemetic for prevention and treatment of postoperative nausea and vomiting in 1970.^{8,9} Droperidol has also been used to manage acute psychosis and acute agitation and as an adjunctive analgesic for migraine headaches.^{10–12} Relative to other first-generation antipsychotics such as haloperidol, droperidol has favorable pharmacologic properties of a faster onset of action and a shorter duration of action, which could allow for faster control of agitation and return to active participation in care.¹⁰ Similar to other first-generation antipsychotics, droperidol can induce extrapyramidal side effects such as dystonia and akathisia.¹¹ In 2001, the FDA issued a boxed warning for droperidol due to concerns over QT prolongation and the risk of arrhythmias.¹² The FDA warning, coupled with drug shortages, resulted in a decline in the use of droperidol in the United States.^{11–13}

In 2015, the American Academy of Emergency Medicine conducted a review of the literature and developed a position statement supporting the use of droperidol for treatment of agitation in the ED.¹¹ In 2016, a Cochrane review also found high-quality evidence supporting the effectiveness of droperidol for treatment of psychosis-induced agitation or aggression and no evidence that droperidol causes more cardiovascular arrhythmias than placebo in adults.¹⁰ However, the effectiveness and safety of droperidol in children remain less well defined. In 2019, a generic manufacturer started to produce droperidol, resulting in a recent increase in availability of droperidol in the U.S. market.¹⁴ In this context, a structured systematic review of current evidence on the effectiveness and safety of droperidol for acute agitation in children is needed.

Goals of This Investigation

The purpose of this study was to systematically evaluate the effectiveness and safety of droperidol for the management of acute agitation in children in acute care settings.

METHODS

Study design

We conducted a systematic review of the effectiveness and safety of droperidol for the management of acute agitation in children in acute care settings following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^{15,16} We registered the study protocol with the PROSPERO International Prospective Register of Systematic Reviews prior to data extraction on February 10, 2021 (registration number CRD42021233313).

Article eligibility criteria

Articles were eligible for inclusion if they reported effectiveness and/or safety outcomes for parenteral droperidol administration for acute agitation in children or youth under 21 years of age in

acute care settings (prehospital, ED, or inpatient medical or psychiatric hospital settings). We defined effectiveness outcomes as time to sedation, depth of sedation, duration of sedation, need for subsequent doses of medication, or utility in preventing patient or staff injury. We defined safety outcomes as adverse medication effects including cardiac arrhythmias, hypotension, hypoxia, need for airway intervention, and extrapyramidal symptoms including dystonic reactions and akathisia. We included articles that examined droperidol administration for the management of acute agitation or that compared its use to another medication for this indication. We noted that the upper age limit for studies of droperidol use in children varied, with at least one article¹⁷ including patients through age 21, so we chose an inclusive approach by selecting age 21 as the upper age limit for article eligibility. We included articles evaluating adult patients if they reported results separately for any subgroup of patients ≤ 21 years old. We included articles that were randomized control trials, systematic reviews or meta-analyses, cohort studies, case-control studies, and case series/reports. We excluded review articles, conference presentations, article commentaries, and articles not written in the English language.

Search strategy

The search strategy was developed by a professional medical librarian. We queried the following databases: CINAHL (EBSCO), the Cochrane Library (Wiley), Embase (Elsevier), Ovid Medline, Pubmed Medline, PsycINFO (EBSCO), Scopus, and Web of Science. The search strategy included four main search themes: pediatric age (e.g., *adolescent or child or pediatric* or youth*), the acute care setting (e.g., *emergency medicine or hospital*), droperidol (e.g., *droperidol or inapsine or droleptan*), and acute agitation (e.g., *agitation* or aggressive* or chemical restraint or dangerous behavior or disrupt* or hostile* or mental health or psychiatric* or violent**). We searched databases from inception through March 31, 2021, limited to English language articles. We hand-searched reference lists of articles meeting inclusion criteria to identify additional citations not returned by the online database searches. We collected references using EndNote (Clarivate, Philadelphia, PA) and managed references using Covidence (Veritas Health Innovation Ltd, Melbourne, Australia).

Article selection

Articles were deduplicated, and titles and abstracts were independently reviewed by two authors (SR and either JH or AP) to assess whether they met article inclusion/exclusion criteria. Discrepancies were resolved by discussion among three authors (SR, JH, and AP), with the author (JH or AP) who did not initially evaluate the abstract serving as the tiebreaker. This process was repeated to determine inclusion/exclusion of full-text articles.

Data extraction and analysis

For included articles, one author (SR, JH, or AP) used a standardized data extraction form to record the study methodology; characteristics of participants; interventions, including specific dosing regimens; and effectiveness and safety outcomes. The same author assessed the article's quality and risk of bias using the Risk of Bias in Non-Randomized Studies of Interventions tool developed by the Cochrane Methods Groups.^{18,19} We chose this tool because all identified articles were observational studies or case reports and not randomized. Three authors (SR, JH, or AP) reviewed the data elements and risk of bias determinations for each article, and differences of opinion were resolved by discussion until consensus was reached.

RESULTS

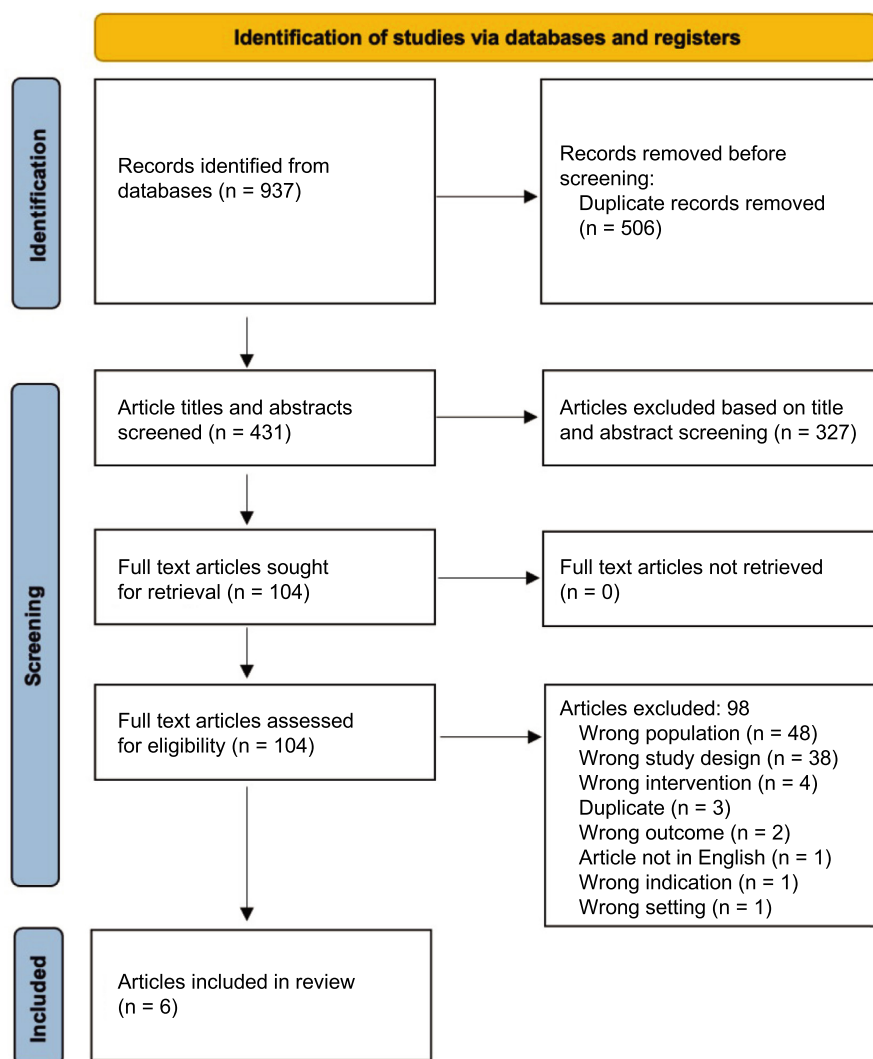
Characteristics of included articles

The search identified a total of 937 citations, with 431 remaining after deduplication. After titles and abstracts were screened, 104 articles remained for evaluation and full-text review. Upon review, six articles met criteria for inclusion (Figure 1).^{17,20-24} Included articles were published between 1998 and 2019. Two articles took place in the prehospital setting, one in the ED, and three in the inpatient hospital setting. Hospital-based studies were each performed at a single academic center, while the largest prehospital study covered a single state's ambulance service. The articles included one prospective observational study, three retrospective observational studies, and two case reports. One case report was a detailed description of a child enrolled in a larger prospective observational study that primarily included adults. The other five articles included children and young adults only. Patients ranged in age from 7 to 21 years old. Aside from the two case reports, sample sizes ranged from six patients²¹ to 96 patients.²⁴ Across the included articles, droperidol was administered to a total of 198 patients under 21 years old, with 241 medication administration episodes. The route was intramuscular, except for 56 episodes of intravenous administration in the study by Szwak et al.¹⁷ No studies compared droperidol to another medication for the management of acute agitation. The study setting, design, participants, and droperidol dosing protocols are summarized in Table 1.

Droperidol dosing protocols

The six included articles reported different droperidol doses, indications for administration, and recommended timing for repeat doses. Three articles reported varying weight-based dosing schemes.^{21,23,24} For patients in the highest weight category, the maximum recommended dose ranged from 3.1 mg²¹ to 10 mg.²⁴ Szwak et al.¹⁷ described a dose range of 1–10 mg with a median

FIGURE 1 Flow diagram of article screening and selection process



dose of 0.14 mg/kg. In the case report by Ho et al.,²² a 112-kg patient received a dose of 5 mg. In the case report by Calver et al.,²⁰ a weight was not reported for a 17-year-old who received a dose of 10 mg.

In two studies, the indication for droperidol administration was based on a standardized agitation severity scale. In Hameer et al.,²¹ droperidol was administered for a level of 3 or greater on the following scale, which was in local use at the institution: (1) sleeping but easily aroused, (2) restless and agitated, (3) physical or verbal hyperactivity with threats of violence, or (4) combative behavior needing physical restraint. In the study by Page et al.,²⁴ droperidol was administered for a Sedation Assessment Tool score of +2 or +3. In contrast to the scale used by Hameer et al., the Sedation Assessment Tool is validated for use in research, with high sensitivity and specificity in predicting the need for additional sedation and high inter-rater reliability.²⁵

Three studies outlined recommendations for repeat dosing. The protocol in Joshi et al.²³ recommended a repeat dose for a lack of response to the initial dose within 30 min, with no more than four doses to be given in 1 day. Similarly, the protocol used in Hameer et al.²¹ stated that doses could be repeated within 15–30 min if

ineffective to a maximum of four doses per day. The protocol in Page et al.²⁴ allowed droperidol administration to be repeated once after 15 min.

Effectiveness outcomes

The articles reported a variety of effectiveness outcomes including time to sedation, depth of sedation, duration of sedation, need for subsequent doses of medication, and utility in preventing patient or staff injury. Page et al.²⁴ reported a median time to sedation of 14 min, with an interquartile range of 10–20 min and range of 3–85 min. Joshi et al.²³ described a range of onset of action of 3–15 min, while Hameer et al.²¹ reported a time of onset of 10–15 min. In the case report by Ho et al.,²² the patient was described as calmer after 6 min.

In terms of depth of sedation, only one of 102 cases (1%) in the study by Page et al.²⁴ resulted in a failure to sedate, defined as an inability to achieve a Sedation Assessment Score decrease by 2 points or a score of zero. Four of six patients who received droperidol in the study by Hameer et al.²¹ were sleeping within

TABLE 1 Characteristics of studies evaluating effectiveness and/or safety of droperidol for acute agitation in children

Reference	Study design	Setting	Sample size ^a	Age (years)	Droperidol dose or dosing protocol	Key efficacy outcomes	Key safety outcomes
Joshi et al. ²³	Retrospective observational	Inpatient	26 patients; 40 administrations	9.1 (mean)	<34 kg: 0.625 mg ^b 34–57 kg: 1.25 mg 57–68 kg: 1.875 mg >68 kg: 2.5 mg Maximum 5 mg	Onset of action: 3–15 min Duration of sedation: 58.5 ± 29.1 min 2 patients required a second dose	One patient with rigidity and two patients with mild extrapyramidal symptoms
Hameer et al. ²¹	Retrospective observational	Inpatient	Six patients; 20 administrations	12.8 (mean)	<35 kg: 1.3 mg 35–55 kg: 1.9 mg 55–70 kg: 2.5 mg >70 kg: 3.1 mg	Onset of action: 10–15 min 4 patients sleeping within 1 h	One patient with hypotension. Some patients experienced drowsiness, nervousness, or restlessness
Szwak et al. ¹⁷	Retrospective observational	ED	68 patients; 73 administrations	19.4 (mean) 13–21 (range)	Median: 0.14 mg/kg Range: 1–10 mg	86.6% achieved effective sedation; 22% of these received more than one dose	No cases of QTc prolongation or arrhythmia on cardiac monitoring
Ho et al. ²²	Case report	Prehospital	One patient; one administration	16	5 mg	Time to sedation: 6 min No subsequent doses No injuries	Maintained normal vital signs
Calver et al. ²⁰	Pediatric case described within prospective observational study	Inpatient	One patient; one administration	17	10 mg	None reported	QTc 505 ms after lamotrigine ingestion
Page et al. ²⁴	Prospective observational	Prehospital	96 patients; 102 ambulance runs; 106 administrations	14 (median) 7–15 (range)	0.1–0.2 mg/kg Maximum 10 mg	Median time to sedation 14 min. 18% required subsequent doses. One patient with failure to sedate. One staff injury	Five patients with hypotension (one received intravenous fluids), two dystonic reactions, one patient with alcohol intoxication and respiratory depression

^aNumber of patients under 21 years old who received droperidol for the indication of acute agitation (studies may have had a larger total sample size) and number of droperidol administration episodes.^bOriginal dosing protocol was reported in pounds and milliliters; we have converted to kilograms and milligrams for ease of comparison.

1 h of administration, while two patients experienced a decrease in agitation to 2 ("restless and agitated") on their scale. In Szwak et al.,¹⁷ 86.6% of cases of droperidol administration resulted in effective sedation, defined as sleeping, calm, resting, cooperative, or quiet. In the case described by Ho et al.,²² the patient was described as "much calmer and quite sleepy" following medication administration.

Two articles reported the duration of sedation attained after the use of droperidol. In one, the mean duration of sedation was 58.5 ± 29.1 min, and all patients were able to return to normal activities within 2 h of droperidol administration.²³ In the case report by Ho et al.,²² the patient slept throughout a 30-min transport to the hospital, except for three transient episodes of awakening with attempts to head-butt staff.

Most patients were adequately sedated after a single dose of droperidol. Page et al.²⁴ found that more than one dose of droperidol was needed to achieve adequate sedation in 21% of 102 cases. Joshi et al.²³ reported that two of 26 (8%) patients required a second dose at 30 min. Szwak et al.¹⁷ found that 22% of patients who were effectively sedated received more than one dose of droperidol. In the case report by Ho et al.,²² the patient required no further doses of droperidol or other medications for sedation during transport or in the ED.

Another reported measure of medication effectiveness was prevention of injuries to the patient or staff. Among the cases of droperidol administration described by Page et al.,²⁴ one injury was sustained by an ambulance staff member and no patient injuries occurred. In the case report by Ho et al.,²² prior to medication administration, the patient had "injured at least one adult on the scene" and "was continuing to injure himself by striking his head against solid objects." After medication administration, the patient did not injure himself or others on the scene or during transport.

Safety outcomes

Reported adverse effects of droperidol included QTc prolongation, hypotension, respiratory depression, and dystonic reactions. Calver et al.²⁰ investigated the cardiac effects of droperidol by measuring QTc intervals obtained from continuous electrocardiogram recordings after droperidol administration. While 46 patients participated in the study, safety outcomes for only one pediatric patient were described. A 17-year-old who presented after an ingestion of 2800 mg lamotrigine was found to have a prolonged QTc of 505 ms on a Holter monitor placed 110 min after she had received 10 mg droperidol. The QT interval was prolonged from the start of monitoring and resolved over several hours. The patient's concurrent lamotrigine overdose precluded definitive attribution of the patient's QTc prolongation to droperidol. In the study by Szwak et al.,¹⁷ all patients received cardiac monitoring from the time of droperidol administration until discharge from the ED, with no patients experiencing an arrhythmia. No other articles reported cases of QTc prolongation or cardiac arrhythmias.

Hypotension and respiratory depression were occasionally noted following droperidol administration. In the study by Page et al.,²⁴ hypotension occurred in five of 102 cases, with four patients experiencing asymptomatic hypotension that resolved without intervention. The remaining patient had a systolic blood pressure of 75 mmHg that responded to intravenous fluids. Hameer et al.²¹ described one case of hypotension in a patient who had also received lorazepam and haloperidol. Among the six included articles, one patient experienced respiratory depression: a patient who presented with alcohol intoxication developed a respiratory rate of 8 and an oxygen saturation of 88% on room air that resolved with supplemental oxygen.²⁴

Dystonic reactions occurred in five out of 198 patients across the six included articles. All cases improved after administration of diphenhydramine or benztropine. Hameer et al.²¹ also described adverse effects of drowsiness, restlessness, and nervousness, but the number of patients who experienced these symptoms was not reported.

Risk of bias assessment

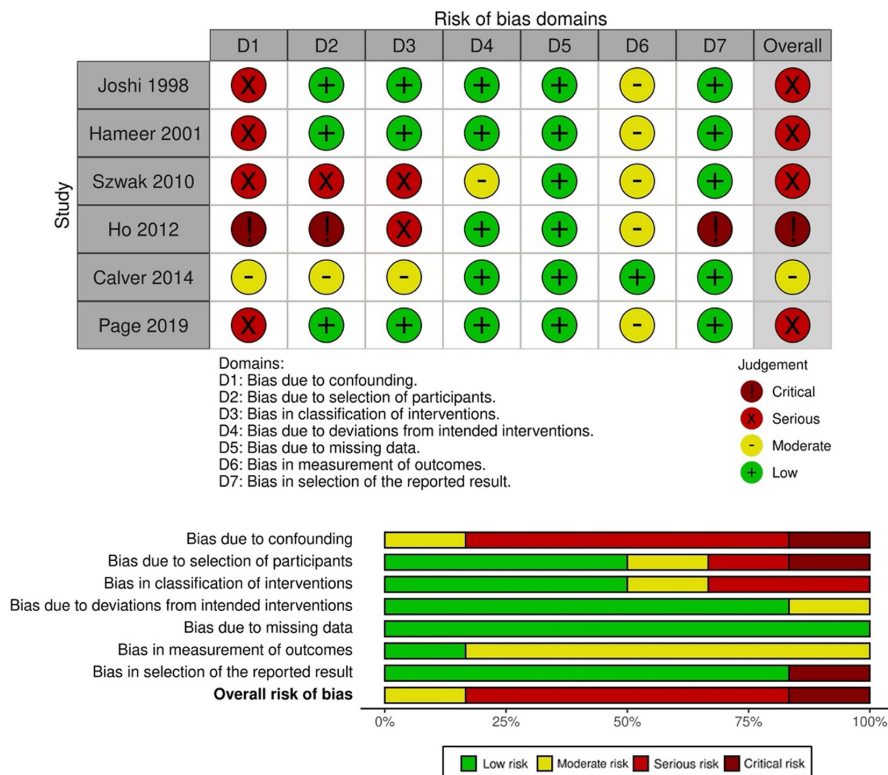
Overall, the risk of bias assessment among the six articles ranged from moderate to critical with the majority of articles falling into the serious risk category (Figure 2). Many of the articles demonstrated a high risk of bias due to observational, unblinded study designs. Many articles demonstrated a high risk of bias due to lack of adjustment for potential confounders. The articles scored low to moderate in risk of bias due to deviations from the intended protocol and missing data.

DISCUSSION

In this systematic review of the use of droperidol for acute agitation in children in acute care settings, we identified six articles that reported effectiveness and safety outcomes. All articles were observational studies or case reports with a moderate to critical risk of bias. No studies directly compared droperidol to another medication in terms of effectiveness or safety. Heterogeneity of definitions for effectiveness and safety outcomes precluded the combination of results in a meta-analysis. Within these limitations, droperidol appears to have a reasonable effectiveness and safety profile that is comparable to other medications currently in use for the management of acute agitation in children.^{5,26}

In the included articles, most patients who received droperidol experienced adequate sedation in under 15 min. Sedation typically lightened at approximately 1 h, with some variation noted. This may present an opportunity for early reassessment of the patient's mental status and ability to reengage meaningfully in care. Additionally, most patients were adequately sedated with a single dose of droperidol and did not require subsequent doses. A wide range of dosing protocols were used, indicating a lack of standardization in practice.

FIGURE 2 Risk of bias for each included article, overall and by specific domains



Despite the FDA boxed warning, only one patient identified in our review developed QTc prolongation. The patient presented with a lamotrigine overdose, and coingestion of other agents could not be excluded.²⁰ While administration of lamotrigine to healthy volunteers is not associated with QTc prolongation,²⁷ QTc prolongation has infrequently been reported in cases of lamotrigine overdose.²⁸ Thus, the patient's prolonged QTc in the study by Calver et al. cannot be definitively attributed to droperidol. A recent prospective study measured changes in QTc intervals after administration of low-dose droperidol in the ED for indications other than acute agitation (primarily given for headache). A modest mean QTc increase of 30ms was observed, with only 4.4% of patients experiencing an increase of ≥ 60 ms. While the findings of this study are reassuring, only two of the 68 patients were under 18 years old; thus the results may not be generalizable to children.²⁹

The most common adverse events described in the included articles after droperidol administration were hypotension (which typically did not require intervention) and dystonic reactions (which responded to anticholinergic medications). One case of respiratory depression occurred in a patient who also had alcohol intoxication. We did not identify any children who developed arrhythmias following droperidol administration.

Droperidol has a history of decades of use for the management of acute agitation. In 2001, the FDA issued a boxed warning regarding the risk of QTc prolongation and arrhythmias; however, clinicians have questioned whether this warning was justified based on available evidence.¹² The warning was placed on the basis of 277 reports of adverse events associated with droperidol use, with 65 individual cases involving at least one cardiac symptom and 35 resulting

in death.¹² However, 135 of the reported adverse events occurred outside of the United States, with doses that were orders of magnitude higher than typical in the United States. Of the five cases of torsades de pointes that resulted in death, four were reported abroad in patients who received 600mg intravenous droperidol.¹² Of note, no cases of torsades de pointes or cardiac arrest were reported in children. The youngest patient with a reported adverse event was an 18-year-old female who developed tachycardia, not otherwise specified.¹²

Our findings on droperidol for acute agitation in children are largely consistent with the evidence base in adults, in which adverse effects of droperidol are rare. In 2015, the American Academy of Emergency Medicine released a position statement on the safety of droperidol use in the ED supported by a literature review.¹¹ Droperidol was found to increase the QT interval in a dose-dependent fashion, and adverse cardiac events were exceedingly rare for low-dose droperidol (<2.5 mg). Intramuscular doses of droperidol up to 10mg were determined to be as safe and efficacious as other medications for acute agitation.¹¹ The position statement recommended that clinicians continue to exercise clinical judgment for patients with underlying susceptibilities such as structural heart disease, concurrent QTc prolonging medications, or familial risk. Additionally, the statement determined there was insufficient evidence to recommend continuous electrocardiogram monitoring after administration of doses of droperidol under 2.5mg.¹¹

Soon afterward, in 2016, a landmark Cochrane systematic review concluded that rates of adverse effects (such as hypotension, respiratory distress, and arrhythmias) were similar between droperidol and other medications for acute agitation in adults.¹⁰ When compared

with haloperidol, droperidol was more likely to result in sedation within 30 min and reduced the risk of needing additional medications for sedation. When compared with midazolam, droperidol was less likely to result in sedation within 30 min, but the midazolam group had more events requiring airway management.¹⁰

Since publication of the Cochrane systematic review, additional evidence continues to emerge describing efficacy and safety outcomes of droperidol for acute agitation in adults. Among 16,546 adults who received droperidol in a large urban ED, mean QTc did not differ before and after medication administration, and only one case of torsades de pointes occurred (incidence 0.006%) in a patient with alcohol use disorder and hypomagnesemia.³⁰ In another large cohort of 5784 patients (with 6881 ED visits) administered droperidol in an academic ED, there were no clinically significant arrhythmias or deaths attributable to droperidol.³¹ In a large retrospective study of adult patients, droperidol led to significantly lower rates of rescue medication use within 1 h than those of haloperidol.³² A prospective observational study of 1257 adults found no difference in time to sedation between droperidol and olanzapine, but did find a higher rate of extrapyramidal adverse effects with droperidol.³³ A randomized controlled trial found that midazolam-droperidol combination was superior to either droperidol or olanzapine monotherapy for sedation of adults with acute agitation,³⁴ while another randomized controlled trial found that droperidol was more effective than lorazepam or ziprasidone for adults with acute agitation and caused fewer episodes of respiratory depression.³⁵ The evidence we identified in children describing effectiveness and safety outcomes of droperidol was much less robust than the corresponding evidence in adults, with no randomized controlled trials identified in children.

LIMITATIONS

There are several limitations to our study. We excluded articles from conference proceedings to ensure that included data passed the standards of peer review required for publication, and we excluded articles not in the English language. These parameters could have limited identification of relevant articles. Additionally, several articles included some children but were excluded from our review because they did not present separate effectiveness or safety outcomes for patients ≤ 21 years of age. Due to substantial heterogeneity in definitions of effectiveness and safety outcomes across articles, we were unable to perform a meta-analysis.

CONCLUSIONS

Reintroduction of droperidol into the U.S. market,¹⁴ along with rising use of medications for acute agitation in children in the ED over the past decade,⁴ have renewed consideration of droperidol as an choice for acute agitation management in children. This systematic review is the first to the authors' knowledge to describe the effectiveness and safety of droperidol for the management of acute

agitation in children in acute care settings. This information is crucial to guide medication choice, when needed to promote patient and staff safety.⁶

In this systematic review, we found limited observational studies and case reports reporting effectiveness and safety outcomes of droperidol for children. In the identified articles, children who received droperidol experienced sedation quickly, with a relatively short duration of effect, which could aid in the prevention of injuries while also allowing a return to participation in the therapeutic milieu. While more robust data are available in adults, we found no pediatric randomized controlled trials that studied droperidol, nor did we identify any observational studies comparing droperidol to other medications used for acute agitation management.

Future research is needed to develop standardized outcome measures for medication effectiveness and safety for acute agitation in children, as standardization would allow for combining results across studies. Additionally, future studies to assess the effectiveness and safety of droperidol in children would benefit from larger sample sizes, more rigorous study designs that reduce the risk of bias, and the inclusion of comparisons against other medications commonly used to manage agitation in children.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Shannon C. Ramsden conceptualized and designed the study, designed the data collection instruments, collected data, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript. Alba Pergjika and Jennifer A. Hoffmann conceptualized and designed the study, collected data, interpreted the data, and reviewed and revised the manuscript. Andrea Fawcett collected data and reviewed and revised the manuscript. Aron C. Janssen, Sukhraj Mudahar, and John T. Walkup conceptualized and designed the study, interpreted the data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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